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EXAMINER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,093	YANNI ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 5-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 5-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments to the claims filed on July 18, 2007 has been received and entered. Claims 1-4 have been cancelled, while claims 6-8 and 15-17 have been amended. Claims 5-22 are under consideration in this application.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited on PTO-1449 or by the examiner on form PTO-892, they have not been considered.

The information disclosure statement (IDS) submitted on 12/13/2005 has been considered by the examiner.

Maintained-Specification

The amendment filed on 12/5/2005 is objected to under 35 U.S.C. 132(a) for introducing new matter into the disclosure 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. In the instant case, the sequence listing filed on 12/5/2005 is not supported by original disclosure.

Maintained-New Matter-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9-13, 14-15 and 18-22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record, advanced in the prior Office action mailed 1/18/07.

37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the recitation of limitation "SEQ ID NO: 1-4" (claims 1, 4, 5, 6, 14, 15) is considered new matter. Applicants do not have support of specific sequence ID No at the time of filing of the specification. Upon further review of the instant specification, examiner could only find references made to SEQ ID NO: 1-4 while describing the invention without providing the actual sequences at the time of filing of instant specification. Thus, the specific sequences set forth in SEQ ID NO: 1, 2, 3, and 4 as recited in claims 1, 4, 5, 6, 14, 15 do not have any explicit support in the specification.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time application was filed...If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application".

To the extent the claimed invention embrace delivering a composition comprising SEQ ID NO: 1-4 that is not described in the instant disclosure. Claims 1-6, 9-13, 14-15 and 18-22 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is noted that Applicants' original disclosure do not teach the sequence comprising Seq ID NO: 1-4 that is

delivered to the eye for the treatment of dry eye condition. As described before, the specification does not provide adequate guidance on determining the specific sequence of SEQ ID NO: 1-4 as embraced by the claims and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

Response to Arguments

Applicants' arguments filed on 07/18/2007 have been fully considered but they are not persuasive. Applicants', in their argument on page 4, state that the present application was filed on June 15, 2005, as a 371 application of PCT/US2003/033139, filed October 17, 2003, which claims priority from provisional application USSN 60/435,988, filed December 20, 2002. The PCT application filed on October 17, 2003, and the 371 application filed on June 15, 2005, are both identical to the provisional application, filed on December 20, 2002.

In response, it is noted that the PCT application filed on October 17, 2003, and the provisional application, filed on December 20, 2002 are identical in content but PCT application failed to incorporate the sequence listing for SEQ ID NO: 1-4 at the time instant application entered into national stage. Thus, there was no support of actual sequence listing in PCT on 6/15/2005. Although, instant application claims priority from the provisional application that included the sequence listing but instant application, which is a 371 application of PCT/US2003/033139, does not appear to state that US provisional application is incorporated by reference in its entirety. Furthermore, there is no evidence that SEQ ID NO: 1-4 in the instant application or PCT, is same as one disclosed in US provisional application, particularly since no sequence listing is provided in these applications. In view of foregoing, it is apparent that SEQ ID NO: 1-4 is described in the specification of the instant application without providing the actual sequences at the time of filing of instant specification. Therefore, rejection is maintained for the reasons of record.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims 5 and 14 encompass a method of treating dry eye in a postmenopausal patient by incorporating nucleic acid encoding 15-lipoxygenase-1, -2 gene products into an *in situ* ocular cell under condition permissive for uptake of nucleic acid such that nucleic acid is expressed and dry eye condition is treated. The dependent claims 6 and 15 recite nucleic acid encoding the gene product. Claims 7-8 and 16-17

limit the cells of claim 6 and 15 respectively to include conjunctiva or corneal epithelial cells that is debrided under conditions permissive for the uptake of nucleic acid such that nucleic acid is expressed and patient is treated. Claims 9-13 and 18-22 encompass viral vector and plasmid for delivering the gene to be expressed in ocular cell as claimed. The subsequent claims limit transgene in either retrovirus or adeno or adeno-associated virus.

The aspects considered broad are the breadth of any subject population, using any method or vector that could be used for treating dry eye condition subsequently limiting to few, any method of administration to affect eye subsequently limiting to drops or ointment, the increase of expression of transgene in many ocular cells then limiting to conjunctival or corneal epithelial cell and transgene not operably linked to expression control elements a critical limitation not described in claims.

The claims 5-22 embrace a method of treating dry eye condition by incorporating into an ocular cell via any route nucleic acid encoding 15-lipoxygenase-1, -2 such that transgene is expressed and the dry eye condition of postmenopausal patient is treated.

The nature of such invention is within the broad genera of gene therapy, and gene therapy is not generally enabling of Applicant's invention due to problems with, *inter alia*, targeting and expression of transgenes at therapeutically effective level by administering composition via any route and method in any specific tissue. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification broadly discloses the need for composition and treatment for dry eye condition particularly in postmenopausal women (pp. 2). The invention is based in part on the discovery that mucin reside in the apical and sub apical corneal epithelium which is secreted via cornea apical, sub apical cells and conjunctival epithelium of human eye (pp 3-4). Page-5 describes different part of the body that produces and secretes mucin and it briefly lists agents that increase mucin and/or tear production. Page-5 broadly tracks claim language. The present inventor discloses that ocular surface epithelium of postmenopausal women lack 15-lipoxygenase. This is required for the synthesis of 15(s)-HETE, which in turn stimulates the production of MUC-1 mucin (pp 6). Pages 7-12 broadly discuss role of lipoxygenase, *in situ* ocular cells, method and type of vector and its use, target ocular cells and permissive condition of nucleic acid uptake for the treatment of dry eye condition.

However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any transgene can be expressed in ocular cells of any subject or human at minimum effective levels for therapeutic response. The specification does not provide any specific guidance for expressing the nucleic acid Seq ID no 1 or 3 at therapeutic effective level in ocular cells of postmenopausal women.

In fact, the art of gene therapy at the time of the filing of this application was unpredictable since numerous factors complicate the gene delivery art that is difficult to be overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101). While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to be desired organs continued to be unpredictable and inefficient.

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

Applicant's examples only describe that 15-Lipoxygenase is expressed in eye. Specifically, Example 1 demonstrates that RP-HPLC analyses of conjunctiva samples showing moderate activity in seven out of 21 samples. The specification discloses four samples that were positive for 15- LO activity for RT-PCR analyses. The results showed only one out of four positive for 15-LO-1 and 1 sample positive for both iso-enzyme (see pages 13-14). It is emphasized that neither art nor instant specification explicitly teach that lack of 15-lipoxygenase-1, -2 in postmenopausal patients result in dry eye condition. The specification on page 6, lines 6-7 states, "... present invention stems from the discovery that the ocular surface epithelium of postmenopausal women may lack 15-lipoxygenase (15-LO) (pp 6, line 7)" suggesting it was just a hypothesis. The art of record only implies potential benefit of supplementing 15-lipoxygenase for the treatment of dry eye condition, however, such an implied statement does not provide specific guidance to practice an unpredictable invention. It is also unclear from the specification whether the example disclosed in the specification uses tissues derived from *ex-vivo* or *in vivo* experiment. In addition, Applicants do not provide any specifics on type of vector or method of delivering or route used to express transgene in the subject exemplified in the specification (see page 14). In addition, it is not enough to reasonably predict that the transgene can be expressed using any vectors delivered via any route at reasonable level for appropriate time duration in appropriate cells of eye for the treatment of dry eye conditions in human or any subject. It is also not apparent how the claimed vectors or other delivery vehicle would be effective in any postmenopausal patients. Artisan could not predict, in the absence of proof to the contrary, that such a method would be efficacious in therapeutic treatment. The specification fails to provide an enabling disclosure for the claimed invention

because the specification fails to provide sufficient guidance as to (1) how an artisan of skill would have practiced the claimed method in any subject or a postmenopausal patient (ii) the claimed method would have resulted in expression of 15-lipoxygenase-1,-2 in amount sufficient to treat the dry eye conditions by administering transgenes via any route in "postmenopausal patient". An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of gene therapy and gene delivery *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

Claims 5-8 and 14-17 are directed to a method for treating dry eye condition by administering a composition nucleic acid encoding a protein set forth in SEQ ID NO: 2 or 4 under condition such that it is expressed. Subsequent claim limit the method to include administering the composition in the topical or ointment form. The specification contemplates contacting an ocular cell with exogenous nucleic acid under conditions that allow the ocular cell to take up the exogenous nucleic acid into the ocular cell and express it. It is noted that specification only teaches that this expression may be accomplished by means familiar to the skilled artisan or methods described in U.S. Patent No. 6, 204, 251 (see page 7, paragraph 3). The specification provides no guidance in terms of whether transgene delivered by methods known in the art would result in expression of 15-lipoxugenase-1 and –2 for adequate time at a level sufficient to elicit pharmacological response. This is particularly important since prior to instant invention, the state of the prior art effectively summarized by the references of Verma and Somia (1997) Nature 389:239-242 and Pfeifer and Verma (2001) Annual Review of Genomics and Human Genetics.2: 177-211 describes progress made in developing new vectors and also suggest vector targeting *in vivo* to be unpredictable and inefficient. Verma et al., reviews various vectors known in the art for use in gene therapy and problems associated with each implying that at the time of claimed invention resolution to vector targeting had not been achieved in the art (Verma et al., 1997; Pfeifer et al., 2001; entire article; IDS). They highlight some advantages of using retroviral and adeno-associated viral vector in gene therapy but also acknowledge a greater level of skepticism in using these vectors in human (Pfeifer et al., 2001; abstract). It is noted by the authors that more efficient and safe vectors are required to deliver gene to the target cell for therapeutic effective level of gene expression (Pfeifer and Verma 2001, Annual Review of Genomics and Human Genetics.2: 177-211, pp 201).

Next, the claims (9-13 and 18-22) recite vectors and plasmid for delivering transgene in ocular cells. The specification teaches that the cornea is readily accessible to gene therapy by injection of naked plasmid DNA into the cornea (see page 7, para. 2). Upon further review, it is noted that Stechschulte, et al. (2001) Investigative Ophthalmology & Visual Science: 42(9): 1975-1979; IDS), teach efficacy and safety of naked plasmid gene therapy to the corneal stroma and epithelium of mice. However, authors also conclude that how broadly these

technique would be applied could be determined only by ongoing work in the art (pp 1978, last paragraph). Thus, while art of record teaches administration of naked DNA to cornea in ocular disease of mice, these findings cannot be extrapolated for a very specific treatment of dry eye condition prevalent in postmenopausal patient. The specification merely provides a general description that is not sufficient to provide enabling support because claimed therapy method cannot be actually reduced to practice until the skilled artisan is provided by sufficient guidance to how much and how long the transgene expression would be required to attain therapeutic response in postmenopausal patients. These methods would have required undue experimentation because neither the specification nor the art of record teaches specific guidance for treating dry eye condition by over expressing 15-lopoxygenase-1, -2 in postmenopausal patients.

Next, Behrens, et al. (2002) Investigative Ophthalmology & Visual Science: 43(4): 968-977, IDS, teaches *in vivo* efficacy and safety of ophthalmic topical treatment of a retroviral vector bearing an antiproliferative dominant negative mutant cyclin G1 (dnG1) construct in corneal haze after phototherapeutic keratectomy (PTK) in rabbit. In addition, Kamata et al., (Mol Ther. 2001, 4(4): 307-312, IDS) teach adenovirus-mediated transduction efficiency in mouse eyes using an adenoviral vector expressing *E. coli* □-galactosidase. It is emphasized that they failed to transfer gene onto the cornea by administering drops of a solution containing adenovirus AxCALacZ. However, direct injection of adenovirus expressing AxCALacZ into the anterior chamber resulted in Lac Z expression in the inner layer of cornea (pp 308, 3rd paragraph).

Martin, et al. (2002) Methods: 267-275, IDS, evinces an optimistic outlook for the treatment of ocular disorder using adneo-associated viral vector (AAVV), but also acknowledges that the art is not yet generally enabling for humans (pp 268 3rd paragraph). It is noted that Martin et al (Methods 2002: 267-275, IDS) emphasize that efficiency of transfection of specific cell types of eye are dependent on a number of variables including the site of injection, the AAV serotype and titer and the amount of DNA (pp 268-269). The specification does not provide any specific guidance to address these issues.

Furthermore, in the instant case, the results of Cuthbertson ('251) or Stechschulte, or Behrens or Kamata or Martin cannot be predictive of treating deficiency of 15-lipoxygenase in treating dry eye condition of postmenopausal patient because above described methods and compositions are used in different animal model for different diseases and therefore cannot be extrapolated to treating a very specific dry eye condition prevalent in specific population of postmenopausal patient. This fact is supported by the fact that no appropriate animal model exists for dry eye condition. In fact, recently Barabino et al., (Investigative Ophthalmology & Visual Science. 2004,45(6): 1641-1646, IDS) describe, "all the existing animal models of dry eye mimic different pathogenic mechanisms of Dry eye syndrome, or keratoconjunctivitis sicca (KCS) and at the moment none of them seems to mirror

precisely the complexity and chronicity of this frequent and debilitating condition" (pp1645; Conclusion). This clearly establishes the unpredictability of the animal models currently being used for evaluating therapeutics effective against dry eye. Therefore, methods of expressing transgene in any other disease model cannot be directly extrapolated to treatment of dry eye conditions in humans. The specification also does not provide any guidance as to how studies in animal model of different disease can be extrapolated to the treatment of dry eye condition in any subject including humans. Furthermore, It is also noted that, the specification does not teach whether viral vectors or plasmid can be used effectively in administering transgene either via any route in postmenopausal patients. In addition, prior art at the time of filing of this application as described before did not provide any convincing guidance in this regard either.

The scope of invention of claims 5-22 encompasses administering the composition using non-viral and viral vector via any or all route of administration (i.e oral, intranasal, intramuscular, intravenous, subcutaneous etc). It has been difficult to predict the efficacy and outcome of transduced therapeutic genes because factors govern the expression and/or therapeutic potential of transduced gene *in vivo* (supra Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101). The transduction of target cells represent the first critical step in any gene based therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. In addition, besides the limitations in gene transfer the problem to selectively target cell s *in vivo* is still one of the most difficult obstacles to overcome. For example, upon systemic administration the viral and non-viral particle may bind to many cells they encounter *in vivo* and therefore would be diluted before reaching their targets. In the instant case, specification does not provide any specific guidance and solely relies on prophetic teachings of prior art that are primarily directed to different methods and treatment different disease. It is noted that neither prior art nor specification provided any guidance whether any or all routes of administration would result in generation of sustained expression of 15-LO-1, -2 at minimum effective level to elicit any pharmacological response in any subject particularly since prior art also disclosed non availability of good animal model to study dry eye conditions.

In reviewing the above-discussed problem, it is evident that the artisan would require, making and/or using a new invention in the field. A showing that enough of 15-lipoxygenase-1, -2 reaches the target cell, enough nucleic acid is incorporated into ocular cells, that such nucleic acid is properly incorporated into such cells as DNA, enough mRNA is produced therefrom, and enough protein is produced and 15-lipoxygenase-1, -2 have an effect on the ocular cells and such effect is enough of an effect for a long enough period of time. Alternatively, direct example of such effect of 15-lipoxygenase-1, -2 would overcome this showing specifically for

15-lipoxygenase-1, -2 if these transgenes are included in the vector they must have met the requirement above.

The cited arts clearly indicate an unpredictable status of the gene therapy art pertaining to treatment of dry eye condition. Although, specific vectors, promoters, genes, and route of administration might be or may have been effective for treatment of specific disease providing specific therapeutic effect. Gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest, which results in a therapeutic effect.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled. The specification and prior art do not teach a method of *in vivo* delivery of a gene such that it is expressed at therapeutic effective level for desired duration in the eye of any subject or postmenopausal patient suffering from dry eye condition. An artisan of skill would have required undue experimentation to develop/design a suitable vector and practice the method as claimed because the art of gene therapy, vector design and *in vivo* delivery and treatment of dry eye condition was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicants' arguments filed on 07/18/2007 have been fully considered but they are not persuasive. Applicants', in their argument on page 6, state that the action's main objection seems to stem from the use of prophetic example. Applicants further assert that majority of the action position relate to the assertion that there is no reasonable predictability of instant type of gene therapy. Applicants also assert that other factors are largely minimized for the purpose of *Wand analysis*. Applicants also cite references of Curtis et al and Pfeifer et al to argue that art of gene therapy has progressed rapidly between 2001 and 2003. In addition, applicants also assert that Pfeifer's assertions appear to go to clinical safety, a matter under FDA jurisdiction.

In response, it is emphasized that the intent of the cited reverences are not to show that a nucleic acid can never be delivered at a site or to an organ for attain a therapeutic response. The Examiner has cited references of Pfeifer et al and Verma

et al to describe the state of gene therapy at the time of filing of this application which indicated that resolution of vector for gene targeting in the treatment of any condition *in vivo* was not predictable. A careful review of the cited reference describes the limitation of administering directly a nucleic acid (non viral vector) or delivering a nucleic acid using any other viral vector intended for a therapeutic response. Specifically, Verma et al states, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression. There are two categories of delivery vehicle ('vector'). The first comprises the non-viral vectors, ranging from direct injection of DNA to mixing the DNA with polylysine or cationic lipids that allow the gene to cross the cell membrane. Most of these approaches suffer from poor efficiency of delivery and transient expression of the gene" (see Verma et al page 239, col. 3, para. 2-3) . Furthermore, Verma describes ".. attempts to deliver genes in viral vectors have been confronted by these host responses". It addition, Pfeifer and Verma emphasize the need for more efficient vectors that are required to deliver gene to the target cell for therapeutic effective level of gene expression (Pfeifer and Verma 2001, Annual Review of Genomics and Human Genetics.2: 177-211, page 201). Furthermore, contrary to applicants' argument, Examiner has supported his arguments with references of Martin, Behrens, Kamata that describes the advancement in the gene therapy art. However, as stated in this and previous office action, the real issue is not whether 15-lipoxgenase-1, -2 could be delivered in eye by various vector as generally argued by the applicants, rather issue at hand is whether enough of protein is made for prolonged period of time for any therapeutic response (see page 15, paragraph 2 of office action dated 1/18/07), and additionally, if the observation of the lack of 15-lipoxygenase is specifically correlated to dry eye in menopausal women (see page 9 second paragraph of the Office action dated 1/18/07). Prior art teaches that numerous factors complicate the gene therapy art that could not have been overcome by routine experimentation. These include, the fate of DNA vector itself,

volume of distribution, rate of clearance in tissue, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101, art of record; Supra). In the instant case, even for the sake of argument, if one assumes that transgene is delivered to ocular cell *in vivo* using any vector or as naked DNA, the specification fails to provide any evidence that enough of protein is being made at the desired site for appropriate duration in any subject to elicit any pharmacological response as discussed before.
Furthermore, Examiner disagrees with Applicants assertion and emphasize that several of Wand factors determinative of enablement rejection were considered in previous office action dated 01/18/2007. The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors were analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled. For instance, the breadth of the claims and the nature of the invention is described on page 4, paragraph 3, bridging to page 7 paragraph 3; the state of the art of gene therapy on page 8 last paragraph to page 9 paragraph 1; the level of predictability in the art on pages 10-14; the amount of direction and guidance provided by Applicant and the existence of working examples on page 9, last paragraph bridging to page 7, first paragraph; and The

quantity of experimentation needed to make and/or use the invention, page 15, paragraph 2). On page 7, applicants argue that safety issue raised in the reference of Pfeifer et al fall within the province of the Food and Drug Administration. In response, it is emphasized that Examiner has no intention to raise any toxicity or safety issue arising from using different vectors for delivery transgene. The discussion is merely intended to address problems that are associated with vector design that differs significantly based on the vector used and the protein being produced (supra). It is noted that neither prior art nor specification provides any specific guidance that delivering transgene by any one of the claimed vector/plasmid that would result in expression of 15-lipooxgenase-1 and-2 in enough quantity for appropriate duration to elicit any pharmacological response. An artisan would have to make a new invention in the field to determine the vector, titer and route that would result in appropriate expression for desired duration in the eye of any post menopausal women suffering form dry eye.

On page 7, paragraph 3, Applicants argue that office action distinguishes Cuthbertson on the grounds that effecting expression in ocular cells is not enabling to treat a disease and that it only teach gene therapy method for nonhuman animal only. Applicants assert that action is contradictory to the teaching of Cuthbertson that describes a method for treating ocular disease in an *in situ* ocular cell that is *in vivo*. It is noted that applicants cite the office action dated march 8, 2006. Applicants argue that issued patent should be presumed valid. Applicants further assert that examiner's analysis of Cuthbertson appears on read the limitation into the claim that is not there. Applicants also argue that gene therapy was a known method of treatment and that its use was believed to be effective at the time of filing of this application (see page 7 paragraph 2).

As an initial matter it appears that applicant's arguments of Cuthbertson is based in response to office action mailed on March 8, 2006 for another copending application (10/688,676) which is now abandoned. It is noted that no office action for

this application was sent in 2006. In the instant case, examiner has used Cuthbertson and others references to indicate that specification contemplates using methods described in U.S. Patent No. 6, 204, 251 (see page 7, paragraph 3). Examiner has provided argument with respect to why one of skilled in the art would have to perform undue experimentation to practice the invention as specification provides no guidance in terms of whether transgene delivered by any known methods would result in expression of 15-lipoxugenase-1 and –2 for adequate time at a level sufficient to elicit any pharmacological response. Furthermore, examiner has also indicated methods and results of Cuthbertson ('251) or Stechschulte, or Behrens or Kamata or Martin cannot be predictive of treating deficiency of 15-lipoxygenase in treating dry eye condition of postmenopausal patient because methods and compositions described in prior art uses different animal model for different diseases and therefore these results cannot be extrapolated to treating a very specific dry eye condition prevalent in specific population of postmenopausal patient.

On page 8, para. 2-3, Applicants argue that Behrens and Kamata have described successful in vivo gene transfer by topical treatment and injection. Applicants argue that applicants have sufficiently established that gene therapy as a viable option and the fact that some experimentation may be necessary does not preclude enablement.

In response, it is again emphasized that the issue is not whether one could deliver transgene in eye rather issue is whether expression of 15-lipoxygenase-1, -2 could be achieved at sustained level in any subject for appropriate time for any therapeutic response. As stated in previous office action, Examiner had summarized his arguments with these three references in conjunction with the teaching of Barabino et al. It is noted that applicants have not presented any argument in this regard. While analyzing the issue of predictability, one cannot solely rely on theoretical basis of beneficial effects of any gene in a therapeutic method. The fact

that Barabino et al., (Investigative Ophthalmology & Visual Science. 2004,45(6): 1641-1646) describe, "all the existing animal models of dry eye mimic different pathogenic mechanisms of Dry eye syndrome, or keratoconjunctivitis sicca (KCS) and at the moment none of them seems to mirror precisely the complexity and chronicity of this frequent and debilitating condition" (pp1645; Conclusion; supra). Barabino et al describes that pathogenic mechanism of dry eye could be multi factorial and could be due to lacrimal inflammation, interruption of neuronal stimulation for tear secretion, defect in membrane and secretory mucin expression, meibomain gland dysfunction. Barabino et al also describe that studies incorporating both intrinsic factors such as immune, endocrine and neuronal and extrinsic factor would provide some advancement in the field of dry eye (see conclusions). It is emphasized that Barabino noted, "there are many variables that influence hormonal effects on lacrimal glands of animals including their species, strain, gender and age to name few". Therefore, in view of above discussion it is apparent that Examiner's analysis of instant claims in view of disclosure of Cuthbertson or Stechschulte, or Behrens or Kamata or Martin cannot be predictive of treating deficiency of 15-lipoxygenase-1, -2 in treating dry eye condition of postmenopausal patient particularly because composition described by Cuthbertson or Stechschulte, or Behrens or Kamata or Martin are different and they have been used in different animal model for different diseases. Therefore, these cited arts couldn't be extrapolated to treating dry eye condition in postmenopausal women as different factors influenced dry eye condition and there was no single predictive animal model as supported by the teaching of Barabino et al (Investigative Ophthalmology & Visual Science. 2004,45(6): 1641-1646; art of record). The specification also does not provide any guidance as to how studies in animal models for a different disease could be can be extrapolated to human situations for the treatment of dry eye as recited in the instant invention. In summary, contrary to applicant's argument neither specification nor prior art teach a method of *in vivo*

delivery of a gene such that it is expressed at therapeutic effective level for desired duration (emphasis added) in the eye of a postmenopausal women suffering from dry eye condition. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).* It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994)*, citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).* Given the breadth of the claims and the guidance provided by the specification it would have required undue experimentation to make and use the method of treating dry eye condition in a postmenopausal patient by one of skill in the art without a reasonable expectation of success.

Withdrawn-Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6-8 and 15-17 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendment to the claims.

Withdrawn-Double Patenting

Claims 5-22 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 5-22 of copending Application No. 10/688,676 is withdrawn in view of abandonment of application number '676.

Conclusion

No Claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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